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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,203	04/25/2000	SUZANNE DE LA MONTE	0609.4370001	2325

7590 09/14/2004

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/14/2004

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/380,203
Filing Date: April 25, 2000
Appellant(s): DE LA MONTE ET AL.

Frank Cottingham

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/2/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that Group I (claims 1, 2, 3, 5, 6, 35); Group II (claims 10, 12, 13); Group III (claims 11, 44, 46, and 47) and Group IV (claim 45) do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

The examiner agrees with appellant's grouping of claims.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Ngo et al., "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox" The Protein Folding Problem and Tertiary Structure Prediction, Merz et al (ed.) Birkhauser, Boston, MA, (1994), pp. 491-494.

Chiu et al., "Optimizing energy potential for success in protein tertiary structure prediction" Folding & Design, vol3 (1998), pp. 223-228

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Upon further consideration the rejection under 112 written description for claim 11 has been withdrawn because claim 11 is limited to SEQ ID NO: 2 and the specification provides written description for SEQ ID NO: 2.

In addition, upon further consideration the rejection under 112 written description for claim 35 has been withdrawn because the specification provides written description for the activities set forth in claim 35.

Claims 1, 2, 3, 5, 6, 10, and 12-13 stand finally rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 3, 5, 6, 10, and 12-13, as best understood, are readable on a genus of a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neurospecific promoter,

and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells, wherein the genus of DNA molecules is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification contemplates a genus of DNA molecules that code for a protein having the activity of SEQ ID NO: 1, which induces neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a host which expresses the DNA sequence (page 18, lines 28-30 and page 20, lines 1-2). The specification provides sufficient description of SEQ ID NO: 1 and a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2. The specification provides sufficient description for a DNA molecule that codes for an AD7c-NTP protein as set forth in SEQ ID NO: 2 when over-expressed in neuronal cells. The art of record teaches that there is a variation within the genus of the claimed DNA molecules. The art of record further teaches that one nucleotide change in a DNA molecule could result in the loss of its biological activity. The essential nucleotides required for an activity of AD7c-NTP are absent from the specification. The specification does not disclose a known correlation between the structure (primary structure) and function of SEQ ID NO: 1 to a genus of claimed DNA molecules. The specification does not provide sufficient description of a genus of DNA molecules with 90% homology to SEQ ID NO: 1 that codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. It is not apparent that on the basis of the applicants' disclosure an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are

essential for the genus of DNA molecules that must exhibit the disclosed biological functions as contemplated by the specification.

The mere contemplation of the claimed genus in the specification is not sufficient to support the present claimed invention directed to a genus of a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neurospecific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of DNA molecules which is at least 90% homologous thereof, that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a DNA molecule, which displays at least 90% homology to SEQ ID NO: 1 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or

simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1, 2, 3, 5, 6, and 35 stand finally rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for a DNA construct, which comprises the DNA molecule of SEQ ID NO: 1 or a DNA molecule comprising a nucleotides sequence encoding the amino acid sequence set forth in SEQ ID NO: 2, wherein said DNA molecule is under control of a heterologous neurospecific promoter and does not reasonably provide enablement for a DNA molecule which is at least 90% homologous to SEQ ID NO: 1 wherein said DNA molecule is under control of a heterologous neurospecific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 10-13 and 44-47 stand finally rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to a DNA construct, which comprises the DNA molecule of SEQ ID NO: 1 or a DNA molecule which at least 90% homologous thereto, wherein said DNA molecule is under control of a heterologous neurospecific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells and a method for screening a candidate drug that is potentially useful for treating Alzheimer's Disease using a host cell transformed with said DNA construct. The field of the invention lies in making a DNA molecule which at least 90% homologous to SEQ ID NO: 1.

The specification contemplates a genus of DNA molecules comprising a nucleotide sequence with 90% homology to SEQ ID NO: 1 or having activity of AD7c-NTP. The specification teaches isolation of AD7c-NTP (SEQ ID NO: 1) from a cDNA library. The specification contemplates that DNA molecules which are 90% homologous to SEQ ID NO: 1 may be isolated from cDNA libraries of human and animals. On pages 45-46 and 48-50 of the specification, assays are contemplated that can be used to identify DNA molecules that encode for proteins that possess activity of AD7c-NTP.

The applicants teach one skilled in the art how to make a DNA molecule comprising the nucleotide sequence set forth in SEQ ID NO: 1 or comprising a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 2. However, the specification as filed does not provide sufficient guidance or factual evidence for one skilled in the art to practice the full scope of the claimed invention. The specification does not disclose which nucleotides of the claimed DNA molecule is considered essential for one skilled in the art to make a representative number of DNA molecules with 90% homology to SEQ ID NO: 1. In view of the art of record and the specification as filed, it is apparent that one skilled in the art would be able to determine a DNA

molecule with 90 percent homology to SEQ ID NO: 1. However, the specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to determine without an undue amount of experimentation to determine if the nucleic acid sequence with at least 90 percent homology to SEQ ID NO: 1, would exhibit the same biological function of SEQ ID NO: 1 (observed activity when the sequence is over-expressed in neuronal cells). Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo et al. The protein folding problem and tertiary structure prediction, 1994, Merz et al (ed.) Birkhauser, Boston, MA pp. 433 and 492-495 and Chiu et al., *Folding and Design*, 1998, pp. 223-228, cited on a prior 892), it would required undue experimentation for one skilled in the art to arrive at other DNA molecules with 90% homology to SEQ ID NO: 1 and having SEQ ID NO: 2 activity when over-expressed in neuronal cells. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other nucleotide sequences that are embraced by the claims. This is the case here. In other words, since it would require undue experimentation to identify other DNA molecules with at least 90% identity to SEQ ID NO: 1 and retaining an activity of SEQ ID NO: 2 when over-expressed in neuronal cells, it certainty would require undue experimentation to make their corresponding DNA and, therefore, one skilled in the art would not enabled to make a genus of DNA molecules

with 90% homology to SEQ ID NO: 1, wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

With respect to the *in vitro* methods contemplated in claims 10-13 and 44-47, the specification does not provide sufficient guidance for one skilled in the art to make and/or use the claimed methods. The specification contemplates an *in vitro* drug screening system. The specification teaches cloning AD7c-NTP into a Lac-Switch expression vector and stably transforming neuronal cells in vitro with said vector. However, the specification does not teach how to distinguish true negatives from false negative or true positives from false positives using the method contemplated in the claimed methods. The specification uses the cDNA of AD7c-NTP, thus most, if not all of the transcriptional and translation control sequences of AD7c-NTP gene are removed from the nucleotide sequence. The control sequences (e.g., heterologous neurospecific promoter) contemplated by the claims are not the same control sequences of the endogenous AD7c-NTP because the sequences are from another gene. The suppression or prevention of expression of the protein coded by the DNA construct in b(i) would reflect interaction with the control sequence and result in false positives/false negatives. Thus, the result of using a promoter/control sequence from another gene would not reflect the activity of the endogenous AD7c-NTP gene.

Furthermore, the specification does not teach how to distinguish an increase in degradation of the protein coded for by the DNA construct from a decrease expression of the protein coded for by the DNA construct. For example, if the candidate drug inhibits expression from the heterologous sequence then the decrease of protein expression would result in both b(i) and b(ii). The specification does not teach an assay for how to distinguish between b(i) and b(ii)

determine if a decrease in level of the protein resulted from degradation of the protein or lack of expression from the promoter. A decrease in expression would not reflect interaction of AD7c-NTP protein with the candidate drug. The specification does not provide sufficient guidance or factual evidence for one skilled in the art to determine if detection of one of the following from step (b)(i)-(iii) is caused by the drug interacting with the non-coding sequence (e.g., promoter); with the AD7c-NTP cDNA, or independently with another gene product in the cultured cells. The art of record is absent for teaching how to determine whether the mechanism caused by the candidate drug is the result of interacting with the promoter, the cDNA, or another protein in the cultured cells. Thus, it would take one skilled in the art an undue amount of experimentation to practice the claimed methods.

In conclusion, the specification as filed and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable one skilled in the art to make a DNA construct, which comprises the DNA molecule of SEQ ID NO: 1 or a DNA molecule comprising a nucleotides sequence encoding the amino acid sequence set forth in SEQ ID NO: 2, wherein said DNA molecule is under control of a heterologous neurospecific promoter and not for the full scope of the claimed invention.

(11) Response to Argument

112 first paragraph written description

Appellants argue that the specification provides detail information on the isolation of the AD7c-NTP (see specification at page 33, line 8 through page 34, line 4) and the specification set forth the complete nucleotide sequence of AD7c-NTP cDNA (SEQ ID NO: 1) and the

specification also describes and illustrates the sequence characteristics and motifs found in the amino acid sequence encoded by SEQ ID NO: 1. See specification at page 34, line 5, through page 35, line 28 and page 7, line 21 through page 8, line 3 and Figure 1. (See pages 14-15).

The argument is not found persuasive because the specification only provides teachings regarding a nucleic acid (SEQ ID NO: 1) or a nucleic acid encoding the AD7c-NTP polypeptide as represented by SEQ ID NO: 2. The specification provides teachings wherein expression of the DNA molecule comprising SEQ ID NO: 1 under control of a heterologous neurospecific promoter results in neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and irregular swollen neurites when over-expressed in neuronal cells *in vitro*. However, claim 1 recites **an activity** of AD7c-NTP when over-expressed in neuronal cells. The activity in claim 1 is broader than the activities observed in the *in vitro* example in the specification as filed and set forth in claim 35. The specification does not teach what nucleotides of a DNA molecule which is at least 90% homology to SEQ ID NO: 1 codes for a protein that **an activity** AD7c-NTP when over-expressed in neuronal cells; for example, there is no structure-function relationship regarding putative DNA molecules encoding AD7c-NTP and having the ability to have **an activity** AD7c-NTP when over-expressed in neuronal cells. There is no description in the instant specification concerning what sequences/structures/domains within the protein are necessary for an activity of AD7c-NTP when over-expressed in neuronal cells. In the absence of a description of what sequences/structures/domains are absolutely required for the protein to have **an activity** AD7c-NTP when over-expressed in neuronal cells, the skilled artisan cannot envision what DNA molecules have at least 90% homology to SEQ ID NO: 1. Therefore,

functional descriptions alone, as recited in claim 1, do not provide any structural information relating to what the recited nucleotide sequences are from claims only reciting such.

Furthermore with respect to the specification and the drawings displaying that the amino acid sequence encoded by SEQ ID NO: 1 has (1) the hydrophobic leader sequence, (2), the myristoylation, (3) **potential** AI cleavage sites, (4) region of **homology** insulin/IGF-1 chimeric receptor, (5) **potential** glycogen synthesis kinase-3, protein kinase C and cAMP or Ca-dependent kinase II phosphorylation motifs (6) the transforming growth factor motif, (7) the sequence exhibit significant **homology** with the A4 alternatively spliced mutant form of NF2, the beta subunit of integrin and the human decay accelerating factor 2 precursor and (8) the sequences that exhibit **significant homology** with human integral membrane protein and myelin oligoglycoprotein-16 (page 7, line 21 through page 8, line 3 of the specification). The specification and prior art do not provide sufficient description for what characteristic(s) listed above result in **an activity** of AD7c-NTP when over-expressed in neuronal cells. More specifically, the specification does not provide sufficient description for how an assertion that the sequence has a **potential** AI cleavage sites or has a **potential** glycogen synthesis kinase-3, protein kinase C and cAMP or Ca-dependent kinase II phosphorylation motifs represents sufficient description of a genus of claimed DNA molecules. Furthermore, the specification does not provide sufficient description for how the sequence having homology or significant homology to a protein (e.g., glycogen synthesis kinase-3, protein kinase C and cAMP or Ca-dependent kinase II phosphorylation motifs, integral membrane protein, myelin oligoglycoprotein, etc.) represents sufficient description of a genus of claimed DNA molecules coding for a protein having **an activity** of AD7c-NTP when over-expressed in neuronal cells.

The specification does not provide sufficient description that the proteins listed above have an activity of Ad7c-NTP when over-expressed in neuronal cells. There is no description in the prior art on the subject of structure-function relationship between the proteins or potential motifs listed above and **an activity** AD7c-NTP when over-expressed in neuronal cells to overcome the deficiencies of the instant specification.

Appellants argue that, "the situation presented in Example 14 of the Written Description Synopsis closely parallels the DNA molecules that are used with or are included within the subject matter of Appellants' claims and the written description provided therefor." See pages 15-20.

The argument is not found persuasive because the specification in example 14 is directed to a protein that catalyzes the reaction of A>B and the claim recites a protein having SEQ ID NO: 3 and variants that are least 95% identical to SEQ ID NO: 3 and catalyzes the reaction of A>B. Appellants' claims recite a DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto, wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. The instant claims recite at least 90% homologous thereto, while the claim in Example 14 recites variants thereof that are at least 95% identical to SEQ ID NO: 3 (amino acid sequence). 90% homology in the claim is different than 95% homology in the example and the claims are broader than the 90% limitation set forth in the claims because the polypeptide sequences embraced by the polynucleotide sequences having 90% homology to SEQ ID NO: 1 can have a substitution of at least 30% of the amino acids of the polypeptides encoded by the claimed DNA molecule. Determining 70% identity at the amino acid level from 90% at the polynucleotide level was based on the following:

substituting 100 nucleotides of a 1,000 base pair polynucleotide sequence is a sequence with 90% identity to the 1,000 base pair polynucleotide sequence. The polypeptide sequence encoded by the polynucleotide sequence with 90% identity would have a polypeptide with 333 amino acids. Substitute one polynucleotide in 100 codons of the polynucleotide sequence with 90% identity would be a polypeptide with 30% substitution.

Furthermore, Example 14 is directed to a protein that catalyzes a specific reaction and the instant claims do not recite a protein that catalyzes a specific reaction (e.g., **an activity** AD7c-NTP when over-expressed in neuronal cells). The specification as filed does not provide sufficient description that the amino acid encoded by SEQ ID NO: 1 catalyzes any reaction. In addition, the specification does not provide sufficient description for procedures for making variants of SEQ ID NO: 1, which has 90% homology and retains an activity of AD7c-NTP when over-expressed in neuronal cells. The USPTO written description guidelines for Example 14 do not correlate to the written description in the appellants' specification as asserted by applicants. Therefore, the specification as filed does not provide sufficient description for a genus of nucleotide sequences with up to 144 different nucleotides (90% homology) to SEQ ID NO: 1 and possesses the biological activity of SEQ ID NO: 1 (AD7c-NTP) when over-expressed in neuronal cells.

Appellants argue that, "in *Enzo*, the Federal Circuit also made specific reference to Example 9 of the Written Description Synopsis. See *Enzo*, 296, F.3d at 1328, 63 USPQ2d at 1615. The analysis set forth in Example 9 further supports Appellants' contention that the written description requirement is satisfied for the claims involved in this appeal and that the rejection was made in error". See pages 20-21.

The argument is not found persuasive because Example 9 is directed to an isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclases activity. The DNA molecule set forth in the claimed invention is not directed to a nucleic acid that encodes a protein that binds a receptor and stimulates a specific activity. Thus, Example 9 does not correlate to the applicants' specification.

Appellants argue that the examiner's statement regarding a variation within a genus cannot be a valid basis for a rejection under 35 USC 112, first paragraph. See pages 22-23.

The argument is not found persuasive because the statement by the examiner is one of the factors set forth in the written description rejection to conclude that the specification as filed was not in possession of the claimed genus of DNA molecule.

Appellants argue that the Examiner's assertion that one nucleotide change in a DNA molecule could result in the loss of its biological activity does not support a rejection for insufficient written description because DNA molecules that have lost their biological activity are outside the scope of the claims on appeal. See page 23.

The argument is not found persuasive because there is no structure-function relationship regarding putative AD7c-NTP polypeptides having an activity of AD7c-NTP when over-expressed in neuronal cells. In the absence of a description of what sequences/structure/domains are required for the protein to the have an activity of AD7c-NTP when over-expressed in neuronal cells from the instant specification, the skilled artisan cannot envision such proteins.

Therefore, the skilled artisan cannot extrapolate to envision the claimed genus of DNA molecules, which encode these proteins.

Appellants argue that in view of the claims including a structure and function, a person of ordinary skill in the art would have been able to easily determine whether a DNA molecule that is under control of a heterologous neurospecific promoter and that is at least 90% homologous to SEQ ID NO: 1 codes for a protein that had an activity of AD7c-NTP when over-expressed in neuronal cells. See pages 23-24.

The argument is not found persuasive because the specification does not describe what sequences/structure/domains are required for the protein to the have an activity of AD7c-NTP when over-expressed in neuronal cells from the instant specification. There is no description in the prior art for what sequences/structure/domains are required for the protein to the have an activity of AD7c-NTP when over-expressed in neuronal cells. Thus, the skilled artisan cannot envision the claimed invention by relying on the teachings in the prior art or the instant specification.

112 first paragraph enablement:

Appellants argue that it would only require routine experimentation for a skilled artisan to obtain the DNA molecules that are encompassed by the invention and DNA molecules that are at least 90% homologous to SEQ ID NO: 1 and that are under control of a heterologous neurospecific promoter could have easily been screened for the ability to code for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. See pages 28-29.

The arguments are not found persuasive because in view of the Wands Factors, the specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a genus of a DNA molecule that is 90% homologous to SEQ ID NO: 1, wherein the DNA molecule encodes a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. The claims embrace a very large number of DNA molecules that is broader than the enabling disclosure because there is no guidance as to which of the nucleotides of a DNA molecule having at least 90% homology to SEQ ID NO: 1 may be changed while the protein encoded by the DNA molecule has an activity of AD7c-NTP when over-expressed in neuronal cells. Furthermore, the amino acid encoded by SEQ ID NO: 1 (1,442 nucleotides) has 375 amino acids (SEQ ID NO: 2) as set forth in the specification and there is no guidance in the specification as to which (if any) of the 375 amino acids may be changed while an activity of AD7c-NTP is retained. The claims are further broader than the 90% limitation set forth in the claims because the polypeptide sequences embraced by the polynucleotide sequences having 90% homology to SEQ ID NO: 1 can have a substitution of at least 30% of the amino acids of the polypeptides encoded by the claimed DNA molecule. Other than SEQ ID NO: 1 encoding the AD7c-NTP protein, the specification fails to disclose any other peptides, which has an activity of AD7c-NTP when over-expressed in neuronal cells. The prior art is silent as to which nucleotides of a DNA molecule comprising SEQ ID NO: 1 are required for the protein encoded by the DNA molecule to have an activity of AD7c-NTP when over-expressed in neuronal cells. Thus, it would require a large amount of undue and unpredictable trial and error experimentation for one skilled in the art to screen DNA molecules comprising a nucleotide sequence with 90% homology to SEQ ID NO: 1 and also meet the functional limitation of the claims.

Appellants argue that the specification provides methods for obtaining DNA molecules, which are at least 90% homologous to SEQ ID NO: 1. See pages 29-31.

The argument is not found persuasive because the enablement rejection is not based on whether or not one skilled in art can obtain sequences exhibiting 90% homology to the claimed sequence. Instead, the enablement rejection is based on the Wands Factors, and given the above analysis of the factors which the Court has determined are critical in determining whether a claimed invention is enabled, it was concluded that the skilled artisan would have needed to have conducted undue experimentation in order to practice the claimed invention. In view of the lack of guidance in the specification as to what 10% of the DNA molecule can be changed while the protein encoded by the DNA molecule maintains an activity of an AD7c-NTP protein when over-expressed in neuronal cells. In addition, there is no indication of what to do with a DNA molecule that has 90% homology to SEQ ID NO: 1, but does not code for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. In view of the lack of guidance in the specification for what nucleotides of SEQ ID NO: 1 are required for the genus of DNA molecule to meet the functional limitation in the claims, the skilled artisan would be required to determine what nucleotides of a DNA molecule encompassed by the genus of DNA molecule are necessary to result in a protein encoded by a DNA molecule having an activity of AD7c-NTP when over-expressed neuronal cells. Thus, appellants do not provide sufficient guidance and/or factual evidence for what DNA molecules with at least 90% homology to SEQ ID NO: 1 code for a protein having an activity of AD7c-NTP when over-expressed in neuronal cells.

Appellants argue that, "the Examiner statement regarding the identification of "essential" nucleotides does not support a rejection for lack of enablement." See page 35.

The argument is not found persuasive because the rejection was based on the Wands Factors and not just whether or not one skilled in the art would require the essential nucleotides to practice the claimed invention. In addition, without the "essential" nucleotides of SEQ ID NO: 1 required for AD7c-NTP activity when over-expressed in neuronal cells, it would require an undue amount of experimentation for one skilled in the art to arrive at other DNA molecules with 90% homology to SEQ ID NO: 1 and having AD7c-NTP activity when over-expressed in neuronal cells. The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation for experimentation in view of the art of record exemplifying the unpredictability of making and using a genus of DNA molecule with 90% homology to SEQ ID NO: 1 that has an activity of AD7c-NTP when over-expressed in neuronal cells, for those skilled in the art to further experiment with DNA molecules with 90% homology to SEQ ID NO: 1 to produce a genus of claimed DNA molecules as intended by the as-filed specification at the time the invention was made.

Appellants argue that a person of ordinary skill in the art could have confirmed that the protein coded by a mutated version of SEQ ID NO: 1 has an activity of AD7c-NTP when over-expressed in neuronal cells using routine methods. See pages 36-37.

The argument is not found persuasive because the claims embrace a very large number of DNA molecules that is broader than the enabling disclosure and the specification and the state of the art, at the time the application was filed, were silent with regard to what DNA molecules that are 90% homologous to SEQ ID NO: 1 could be used in the screening assay. The specification does not teach a structure-function relationship between the nucleotides of SEQ ID NO: 1 and an activity of AD7c-NTP when over-expressed in neuronal cells. Furthermore, Appellants' argument indicates that one skilled in the art would have to perform trial and error experimentation on each mutated version of SEQ ID NO: 1 to determine which mutated version of SEQ ID NO: 1 has an activity of AD7c-NTP when over-expressed in neuronal cells. See MPEP 2164.05(a), which recites that the specification must be enabling of the filing date. Thus, if the guidance in the specification requires one skilled in the art to perform trial and error experimentation on each mutated version of SEQ ID NO: 1 to determine which version meets the structural limitation of the claims, this would indicate that the specification was not enabling as of the filing date.

Appellants further argue that it would have been routine in the art to make DNA molecules that encompassed by or included within the subject matter of the claims and test them for the ability to encode proteins that possess AD7c-NTP activity when over-expressed in neuronal cells. See pages 36-37.

The argument is not found persuasive because of the reasons set forth above. More specifically, there is no guidance in the specification as to what 10% of the DNA molecule can be changed while maintaining activity of AD7c-NTP protein when over-expressed in neuronal cells. Based on the lack of teaching in the specification and the prior art for what nucleotides of

the DNA molecule set forth in SEQ ID NO: 1 are required for coding for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells, one skilled in the art would require a large amount of undue and unpredictable trial and error experimentation to determine what sequences with 90% homology to SEQ ID NO: 1 and are under control of a heterologous neurospecific promoter also have an activity of AD7c-NTP when over-expressed in neuronal cells.

Appellants argue that:

> The examiner has not clearly explained what is meant by "false positive" and "false negative. It appears, however, that the term "false positive" was intended to mean drug candidates that suppress gene expression by interacting with the heterologous neurospecific promoter but would not suppress the expression of AD7c-NTP in its normal cellular environment. Similarly, it appears that the term "false negative" was intended to mean drug candidates that do not suppress expression from the heterologous neurospecific promoter but would nonetheless suppress the expression of AD7c-NTP in its normal cellular environment. See pages 43-44.

The appellants' interpretation of the meaning of the terms "false positive" and "false negative" is correct.

Appellants argue that, "the error in the examiner's reasoning is that the claims are directed to methods for screening *potentially* useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas or gliblastomas." A drug that results in any of the detections steps listed in the claimed methods even if it does by

interacting with the heterologous neurospecific promoter would be a candidate drug. See pages 43-46.

Appellants' argument is not found persuasive because the specification uses the cDNA of AD7c-NTP, thus most, if not all of the transcriptional and translation control sequences of AD7c-NTP gene are removed from the nucleotide sequence. The specification and the prior art do not teach that the control sequences (e.g., heterologous neurospecific promoter) contemplated by the specification are the same control sequences of the endogenous AD7c-NTP. The result of using a promoter/control sequence from another gene would not reflect the activity of the endogenous AD7c-NTP gene. In addition, the specification and the prior art do not teach what types of heterologous neurospecific promoters are associated with Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas or gliblastomas. Thus, if the result of the candidate drug in any of the detection steps is caused by interacting with the promoter, one skilled in the art would have to further experiment without guidance from the specification or prior art to determine whether the promoter is associated with a disease recited in the claims. See MPEP 2164.05(a), which recites that the specification must be enabling of the filing date. Thus, if the guidance in the specification and in the prior art for determining whether the result of the candidate drug was caused by interaction with the heterologous promoter or the mRNA of the cDNA is not available, one skilled in the art would have to perform an undue amount of experimentation to determine whether the result of the drug was caused by interaction with the promoter or interaction with the mRNA of the cDNA. This would indicate that the specification was not enabling as of the filing date.

Appellants' further argue that the examiner's assertion that the claimed method would identify false positives and false negatives is flawed because it assumes that a drug that suppresses or prevents protein expression would do so only by interacting with the heterologous neurospecific promoter and the interaction could result through another mechanism other than the promoter, e.g., stimulate degradation of the mRNA, reduce stability of the mRNA, or interfere with translation of the mRNA. See page 46.

Appellants' argument is not found persuasive because while it is acknowledged that interactions with drug could result through another mechanism other than the promoter, the specification as filed does not teach one skilled in the art how to determine whether the suppression or prevention of the expression of the protein was the result of an interaction of the drug with the heterologous promoter or with the mRNA of the claimed DNA molecule. The prior art is silent with regard to how to determine whether the interaction was the result of the heterologous promoter or the mRNA. Therefore, the skilled artisan could not consult the prior art to make and use the instant invention. In view of the lack of guidance in the specification for how one skilled in the art can determine whether the interaction was with either the promoter or the mRNA of the DNA molecule, the skilled artisan would be required to further experiment to determine whether the drug is a candidate for a disease associated with the promoter or a candidate for a disease associated with the protein encoded by the claimed DNA molecule.

Appellants' argue that although the specification does not explicitly describe how one of ordinary skill in the art would go about distinguishing an increase in protein degradation from a decrease or suppression of gene expression, such methods are basic techniques in the field of

molecular biology and would have been known and available to persons of ordinary skill in the art at the time of the effective filing date of the application. See pages 47-52.

Appellants' argument is not found persuasive because the enablement rejection is not based on whether or not is was known how to distinguishing an increase in protein degradation from a decrease or suppression of gene expression, the rejection was based the skilled artisan would be required to further determine whether the drug is a candidate for a disease associated with the promoter or a candidate for a disease associated with the protein encoded by the claimed DNA molecule. The specification does not provide sufficient guidance or factual evidence for one skilled in the art to determine if detection of one of the following from step (b)(i)-(iii) is caused by the drug interacting with the non-coding sequence (e.g., promoter); with the AD7c-NTP cDNA, or independently with another gene product in the cultured cells. The art of record is absent for teaching how to determine whether the mechanism caused by the candidate drug is the result of interacting with the promoter, the cDNA, or another protein in the cultured cells. Thus, it would take one skilled in the art an undue amount of experimentation to practice the claimed methods.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

BW
September 8, 2004

Conferees

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